REMARKS

Claims 1-8, 10-30, 34, 38-41, and 44-61 are pending in the instant application. Applicants request amendment of claims 1, 50, and 52-55 according to the Listing of Claims above, as well as cancellation of claim 61 without prejudice or disclaimer. Upon entry of the present Amendment, claims 1-8, 10-30, 34, 38-41, and 44-60 will be pending in the application.

The claims have been amended to correct certain typographical errors. For example, in claim 1, the locant "6" was added to the name of the compound "N-benzyloxycarbonyl-L-aspartic acid 2,6-dichloro-3-(benzyloxy)benzoyloxymethyl ketone" in order to correct the name of this compound. Amendment and cancellation of the claims herein should in no way be construed as acquiescence to any of the rejections/objections set forth in the instant Office Action, or in any previous Office Action, and were done solely to expedite prosecution of the above-identified application. Applicants reserve the option to prosecute the same or similar claims as those originally filed in the instant application or one or more or subsequent applications. No new matter has been added.

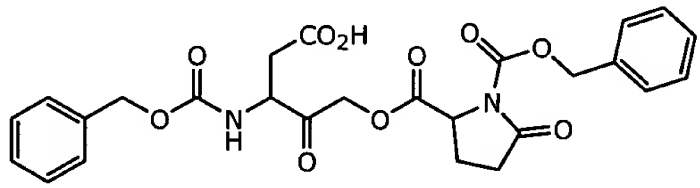
Claim Objections

The Office Action indicates that should claim 55 be found allowable, claim 61 will be objected to as a substantial duplicate of claim 55. Claim 61 recites the pharmaceutically acceptable prodrug of a compound of Formula I according to claim 55. Claim 55 is directed to a pharmaceutically acceptable ester, amide, or prodrug of a compound of Formula I according to claim 1. Therefore, claims 55 and 61 are not duplicates. In reviewing the claims, Applicants note that claim 58 and claim 61 appear to be substantial duplicates of each other. Therefore, Applicants surmise that Examiner meant claim 58, instead of claim 55. Nevertheless, the objection is moot in view of the cancellation of claim and 61.

Rejection of Claims 1 and 18 under 35 U.S.C. § 112, Second Paragraph

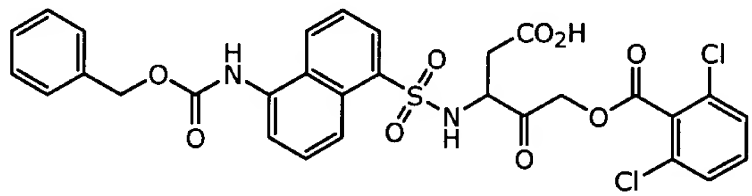
Claims 1 and 18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. With regard to claim 1, the Office Action indicates that the claim has been amended so that it does not allow for esters, but the proviso includes esters. Applicants respectfully traverse the rejection.

Applicants note that claim 1 was amended to delete the recitation of ***pharmaceutically acceptable esters*** thereof; *i.e.*, compounds of Formula I that are pharmaceutically acceptable and have at least one functional group that has been esterified. Dependent claims were added to capture this recitation. For example, the compound of Example 1zz on page 72 of the instant application, shown below and specifically recited in claim 31, is an ester (specifically, it is a benzyl ester).



Example 1zz: *5-Oxo-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-(3-benzyloxycarbonylamino-4-carboxy-2-oxo-butyl) ester*

Furthermore, one of ordinary skill in the art will readily appreciate that the ester compound of Example 1zz is β-carboxylic acid (*i.e.*, it has a free 4-carboxy group) that could be esterified to arrive at a pharmaceutically acceptable ester. The structure of one of the ester compounds in the proviso of claim 1 is shown below.



2,6-dichloro-benzoic acid 3-(5-benzyloxycarbonylamino-naphthalene-1-sulfonylamino)-4-carboxy-2-oxo-butyl ester

Like the compound of Example 1zz, it too has a free 4-carboxy group that could be esterified to arrive at a pharmaceutically acceptable ester.

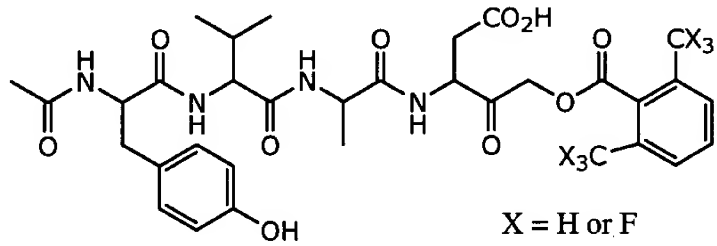
Therefore, Applicants submit that the claim is not indefinite because the proviso includes ester compounds. For purposes of clarification, claim 55 has been amended to recite "A pharmaceutically acceptable ester, amide, or ***other*** prodrug of a compound of Formula I according to Claim 1, wherein..."

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

Claim Rejections - 35 U.S.C. § 102

Rejection of Claims 1, 10, 30 and 52 under 35 U.S.C. § 102(b) over Thornberry I

Claims 1, 10, 30 and 52 are rejected under 35 U.S.C. § 102(b) as anticipated by Thornberry, *et al., Biochemistry* 33(13), 3934-40 (1994) ("Thornberry I"). The Office Action sets forth the allegation that compounds 1 and 2 on page 3937 of Thornberry I fall with the scope of claims 1, 10, 30 and 52. Compounds 1 and 2 have the following structures:



Compound 1: *[X = F] 2,6-Bis-trifluoromethyl-benzoic acid 3-(2-{2-[2-acetylamino-3-(4-hydroxy-phenyl)-propionylamino]-3-methyl-butyrylamino}-propionylamino)-4-carboxy-2-oxo-butyl ester*

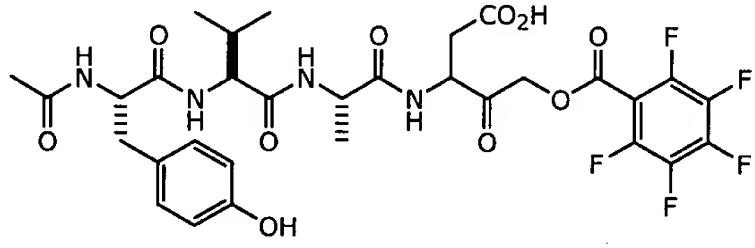
Compound 2: *[X = H] 2,6-Dimethyl-benzoic acid 3-(2-{2-[2-acetylamino-3-(4-hydroxy-phenyl)-propionylamino]-3-methyl-butyrylamino}-propionylamino)-4-carboxy-2-oxo-butyl ester*

In order for the compound to fall within the scope of the claim, the R^2 group would be a trifluoromethyl-substituted phenyl group. Such an R^2 group is not possible according to the proviso that "the aryl group is not substituted with . . . trifluoromethyl" as recited in, for example, claim 52. Applicants submit that Thornberry I does not anticipate the claims as presented herein. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 55 and 56 under 35 U.S.C. § 102(b) over Chapman

Claims 55 and 56 are rejected under 35 U.S.C. § 102(b) as anticipated by U.S Patent No. 5,430,128 to Chapman, *et al.* ("Chapman"). The Office Action alleges that Chapman

discloses, in the text bridging columns 17-18, the benzyl ester of the compound depicted below, and that this benzyl ester falls within the scope of claims 55 and 56. Applicants respectfully disagree. The compound bridging the bottom of column 17-18 is the benzyl ester of the aspartic acid in the following structure:



N-(N-acetyl-tyrosinyl-valinyl-alaninyl)-3-amino-4-oxo-5-pentafluorobenzoyloxy pentanoic acid

Applicants has previously shown, in their submission dated January 24, 2003, that the compounds of Chapman are not within the scope of claim 1. Because claim 55 specifically makes reference to the compound of Formula I of claim 1, then claim 55 does not include the benzyl ester of the above-shown compound because the carboxylic acid has been excluded from claim 1, and therefore Chapman cannot anticipate claim 55 or claim 56 depending therefrom. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim Rejections - 35 U.S.C. § 103

In order to establish a *prima facie* showing of obviousness over the prior art, Examiner must show the following three elements: (1) a suggestion or motivation to combine or modify the cited references; (2) a reasonable expectation of success; and (3) that the combination or modification of the prior art references teaches all the limitations of the claim at issue. Failure to show any one of the foregoing negates a *prima facie* showing. The initial burden is on Examiner to provide some suggestion of the desirability of doing what the inventor has done. *See*, M.P.E.P. § 2142 *et seq.*

Whether the rejection for obviousness depends on a combination of prior art references or a single reference alone, there must be some teaching, suggestion, or motivation to combine or modify the references. Usually, the suggestion comes from the teachings of the pertinent references, or from the ordinary knowledge of those skilled in the art that certain references are of special importance. It is clear that the suggestion or motivation cannot be derived from the

teachings of the applicant. Therefore, when examining the patentability of a claimed invention that combines known elements, "the question is ***whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination***." *In re Rouffet*, 149 F.3d 1350, 1355-56 (Fed. Cir. 1998) (emphasis added); *see also*, *GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1462 (Fed. Cir. 1984); and *In re Beattie*, 974 F.2d 1309, 1311-12 (Fed. Cir. 1992). In other words, it not sufficient that the prior art ***could*** be so modified. Rather, the prior art must teach or suggest that the prior art ***should*** be modified. *See*, *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984).

Merely identifying all of the elements of a claim or their equivalents in the prior art is not sufficient. Almost all inventions are combinations of old elements, and an examiner may often find every element of a claimed invention in the prior art. If this finding were sufficient "to negate patentability, very few patents would ever issue." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). Therefore, in order to establish a *prima facie* rejection for obviousness, an "***examiner must show reasons*** that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would [*not* could] select the elements from the cited prior art references for combination in the manner claimed." *Id.*

Although the references cited under section 103(a), discussed below, teach specific ICE inhibitors and related compounds, none of the references explicitly or implicitly suggests that particular structural features of the distinct ICE inhibitors should be combined in the specific pattern recited in the instant claims. In other words, the cited references, alone or in combination, neither teach nor suggest that a particular first element of the ICE inhibitors of one reference should be combined with a particular second element of the ICE inhibitors of another reference to arrive at the compounds recited by the instant claims.

Rejection of Claims 1, 10, 21, 24-26, 30, and 52 under 35 U.S.C. § 103(a) over Thornberry I

Claims 1, 10, 21, 24-26, 30, and 52 are rejected under 35 U.S.C. § 103(a) as unpatentable over Thornberry, Biochemistry, *op cit.* (Thornberry I). Applicants respectfully traverse the rejection.

Examiner, relying on the first and last paragraphs of the reference, indicates that the reference suggests that the compounds disclosed therein have utility in inhibiting ICE, and also expressly suggests the use of these compounds in the treatment of inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. However, Examiner acknowledges that the reference does not specifically exemplify treatment of these diseases. Examiner concludes

that it would have been obvious to administer the compounds of the reference for treatment of diseases wherein the inactivation of interleukin-1 would be beneficial, including inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. Examiner also indicates that one of ordinary skill would reasonably expect success in the use of these compounds for such treatment.

First, the claims as presented herein do not read on any of the compounds disclosed in the Thornberry reference. Moreover, Examiner has not pointed to any teaching or suggestion whatsoever that would provide the requisite motivation to one of ordinary skill in the art to modify the structures of the Thornberry compounds to arrive at the instantly claimed compound. The reference neither explicitly nor implicitly suggests that particular structural features of the distinct ICE inhibitors should be combined in the specific pattern recited in the instant claims. In other words, the cited reference neither teaches nor suggests that a particular first element of an ICE inhibitor should be combined with a particular second element of another ICE inhibitors to arrive at the specific combination recited by the instant claims. The reference does not teach all of the choices for these elements, as recited in the claims, or which combinations to use to arrive at the claimed compounds. Thus, the reference does not put one of ordinary skill in possession of the invention as claimed.

Examiner relies on the first paragraph of the reference, which provides in pertinent part:

> "Interleukin-1 (IL-1) has been implicated in the pathogenesis of several acute and chronic inflammatory diseases, including rheumatoid arthritis, inflammatory bowel disease, and septic shock. . . . Evidence for a major role for this enzyme in inflammation has recently been provided by the cowpox virus . . ."

However, as admitted by Examiner, the reference does not expressly teach treatment of these diseases. Therefore, Examiner's position is that it would be obvious to try using these compounds for the treatment of such diseases. However, it is well known that "obvious to try" is not the test of obviousness under 35 U.S.C. § 103. Rather, the reference must teach that the compounds should be used to treat such diseases.

Examiner also relies on the last paragraph of the reference which provides in part:

> "It is not yet clear that ICE is an appropriate target for therapeutic intervention in inflammatory diseases. Although

> studies with IL-1 receptor agonist indicates that IL-1 is a major mediatory of inflammation . . ., the relative contributions of IL-1α and IL-1β *in vivo* have yet to be determined. While the recent discovery of cowpox virus ICE inhibitor (crmA) establishes the importance of ICE, and thus IL-1β, in the host response to infection, it also raises serious questions as to the safe administration of ICE inhibitors."

Examiner takes the position that one of ordinary skill would reasonably expect success in the use of these compounds for such treatment. However, based on the foregoing excerpt, with all its uncertainties and cautions, one of ordinary skill in the art would not have a reasonable expectation of success in using the compounds for treatment of inflammatory diseases.

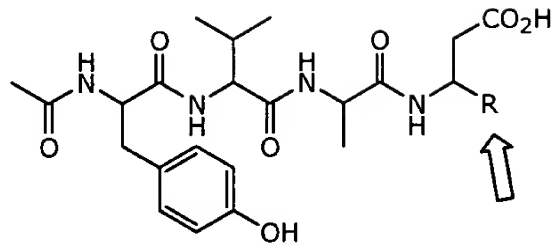
Rejection of Claim 22 over Thornberry I in view of Thornberry II

Claim 22 is rejected under 35 U.S.C. § 103(a) as unpatentable over Thornberry, Biochemistry, *op cit.* ("Thornberry I") as applied to claims 1, 10, 30 and 52 above, and further in view of Thornberry, *et al.*, Perspectives in Drug Discovery and Design 2, 389-99 (1994) ("Thornberry II"). Applicants respectfully traverse the rejection.

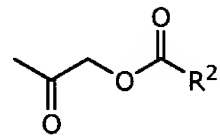
The Office Action, at page 5, indicates that Thornberry I does not teach the inhibition of caspase-4, also known as ICE_{rel}-II, and that Thornberry II teaches that ICE and ICE_{rel}-II are in the same family of closely related cysteine proteases. Examiner notes that both ICE and caspase-4 have utility in the inhibition of the activity of interleukin-1. Alleging a close relationship between these enzymes (citing the paragraph bridging pages 393 and 394 and Figure 2), Examiner concludes that it would have been obvious to one having ordinary skill in the art to use the compounds taught by Thornberry I for inhibiting caspase-4 and that one of ordinary skill would have a reasonable expectation of success in this use.

Thornberry I was distinguished above and those remarks are reiterated here. Examiner admits that the reference does not teach the inhibition of caspase-4.

Thornberry II discloses 6 compounds (shown in Figure 1 on page 392) that are reported to be potent and selective reversible and irreversible peptide-based inhibitors for ICE. These structure and activity of these compounds are discussed in the context of structural parameters that might someday be used to design inhibitors that are efficacious *in vivo*. The six compounds disclosed in the reference have the following generic formula:



wherein R (noted by the arrow) is defined in Figure 1. Upon a review of the definitions of R, it is clear that compounds 1-5 are not related to the claimed compounds because in accordance with Formula I of the instant claims, the R substituent would have to be the following moiety:



wherein R^2 is defined as in claim 1. Although compound 6 contains this element wherein R^2 is a 2,6-dimethylphenyl moiety, compound 6 is specifically excluded from the claims by proviso.

Thus, the claims as presented herein do not read on any of the compounds disclosed in Thornberry II. Moreover, Examiner has not pointed to any teaching or suggestion whatsoever that would provide the requisite motivation to one of ordinary skill in the art to modify the structures of the Thornberry II compounds to arrive at the instantly claimed compound. The reference neither explicitly nor implicitly suggests that particular structural features of the distinct ICE inhibitors should be combined in the specific pattern recited in the instant claims. In other words, the cited reference neither teaches or suggests that a particular first element of the ICE inhibitors should be combined with a particular second element of the ICE inhibitors to arrive at the compounds recited by the instant claims. The reference does not teach all of the choices for these elements, as recited in the claims, or which combinations to use to arrive at the claimed compounds. Thus, the reference does not put one of ordinary skill in possession of the invention as claimed.

Examiner also states that if a patient had a condition requiring inhibition of caspase-4, one of ordinary skill would reasonably expect that they would also be in need of inhibition of ICE, so even if every compound known to inhibit ICE were not an inhibitor of caspase-4, it would be expected to provide relief by inhibiting the action of interleukin 1. Clearly, this statement and Examiner's entire obviousness argument is based on Examiner's position that

because ICE and caspase-4 are members of the same family, a compound that inhibits one will also inhibit the other, thereby inhibiting the action of interleukin-1. Applicants disagree.

Examiner admits that Thornberry I does not teach the inhibition of caspase-4. Also, Applicants have been unable to find anything in Thornberry II that teaches or suggests that the six compounds shown in Figure 1 in fact were capable of inhibiting caspase-4. There is but a passing reference to ICE_{rel}-II (caspase-4) on page 393 in the context of a class of cysteine proteases that include ICE and ICE_{rel}-II. In fact, the reference seems to suggest that only ICE was tested. See page 396, last full paragraph, first sentence.

In support of her position, Examiner cites the disclosure at page 393, second paragraph, that members of this class of cysteine proteases have highly conserved sequences at their active sites with an unusual specificity for aspartic acid in the S_1 cite. However, that paragraph also indicates that:

> "the homology between family members does not appear to extend to the S_4 subsite, ***a critical determinant for ICE***, suggesting that ***these proteases will have distinct extended substrate specificities***. This has indeed proven to be the case for ICE and cPP32, the two human homologues that have been extensively characterized... ***The ability to synthesize inhibitors that are specific for a particular family member will clearly be important with respect to development of therapeutically beneficial inhibitors of these enzymes***, given the preliminary indications that these proteases function in diverse biological processes." (Emphasis added.)

Based on this, one of ordinary skill in the art would not expect ICE and caspase-4 to behave the same way upon exposure to the compounds of the reference. Indeed, Applicants' discovery that the compounds of the invention are capable of inhibiting caspase-4 is truly surprising.

Moreover, the reference clearly teaches away from the invention. The compounds of the invention are peptide inhibitors. However, the reference, at page 396, last full paragraph, indicates that "the challenges that remain are to develop ***non-peptide*** inhibitors that are stable, bioavailable, and more effective than the present [peptide] inhibitors." (Emphasis added).

Rejection of Claims 24-26, 28, and 29 over Thornberry I in view of Bemis

Claims 24-26, 28, and 29 are rejected under 35 U.S.C. § 103(a) as unpatentable over Thornberry I as applied to claims 1, 10, 30 and 52 above, and further in view of U.S. Patent No. 5,843,904 to Bemis, *et al.* ("Bemis"). Applicants respectfully traverse the rejection.

The Office Action at page 6 indicates that Bemis teaches that ICE inhibitors are useful for treatment of diseases taught by Thornberry I, such as arthritis and IBD, as well as stroke, Alzheimer's disease, and shigellosis. Examiner takes the position that it would have been obvious to one of ordinary skill in the art to use the compounds taught by Thornberry I for the treatment of stroke, Alzheimer's disease and shigellosis, and that one of ordinary skill would have a reasonable expectation of success in the use of these compounds for the treatment of these disorders in view of the teachings of Bemis that ICE inhibitors have utility in such treatment.

Thornberry I was distinguished above and those remarks are reiterated here. Examiner has admitted on page 4 of the Office Action that Thornberry I does not disclose treatment of diseases inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease.

Bemis is directed to compounds that are inhibitors of ICE and to the use of the compounds for the treatment of IL-1 and apoptosis-mediated diseases. The patent neither teaches nor suggests the compounds of the invention. In fact, the compounds of Bemis are significantly structurally distinct from those of the invention, because the Bemis compounds lack the aforementioned structural feature, *i.e.*, $-(CO)CH_2(O_2C)R^2$, found in claimed compounds. Moreover, there is nothing in the reference that suggests that the compounds lacking this feature would be structurally and functionally equivalent to the claimed compounds, such that one of ordinary skill in the art would be motivated to modify the Bemis compounds to arrive at the claimed compounds, and would reasonably expect them to have the same activity.

Furthermore, Thornberry I does not make up for the deficiencies of Bemis. Compounds 1 and 2 of Thornberry I also have the above-mentioned structural feature that the Bemis compounds lack. As there is nothing in either reference that suggests that the compounds lacking this feature would be structurally and functionally equivalent, one of ordinary skill in the art would not be motivated to combine the references.

As noted above, the Thornberry reference does not disclose treatment of diseases such as rheumatoid arthritis and inflammatory bowel disease. The Thornberry reference, at most, contains a passing reference to the fact that IL-1 has been implicated in the pathogenesis of several acute and chronic inflammatory diseases, including rheumatoid arthritis, inflammatory

bowel disease, and septic shock. However, there is no mention in the reference that IL-1 has been implicated in stroke, Alzheimer's disease and shigellosis. Thus, absent the teachings of the instant application, one of ordinary skill in the art would have no motivation to combine the references in the manner suggested in the Office Action.

Furthermore, one of ordinary skill in the art would not have a reasonable expectation of success in using the compounds for treatment of inflammatory diseases, let alone stroke, Alzheimer's disease and shigellosis. In this regard, Examiner's attention is again invited to the above-quoted excerpt from the last paragraph on page 3940 of the Thornberry I reference.

Rejection of Claims 1, 10, 11, 21, 24-27, 30, and 52-56 over Chapman

Claims 1, 10, 11, 21, 24-27, 30, and 52-56 are rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent 5,430,128 to Chapman, *et al.* Applicants respectfully traverse the rejection.

Examiner alleges that the patent expressly suggests the preparation of many more compounds (than those explicitly disclosed herein) *via* a simple change at various sites on the generic molecule disclosed in the patent. Examiner then describes a number of substitutions that could be made to yield the compounds encompassed by the claims of the application.

Merely identifying all of the elements of a claim or their equivalents in the prior art is not sufficient. In order to establish a *prima facie* rejection for obviousness, an ***examiner must show reasons*** that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, ***would*** (***not*** could) select the elements from the cited prior art reference to arrived at the compounds claimed.

Applicants made arguments to distinguish the Chapman patent from the instant claims in the previous Office Action (Paper No. 28), and reiterate the substance of those arguments here. Applicants also assert that Examiner merely alleges through conclusory statements that the compounds of Chapman ***could*** be modified to arrive at compounds encompassed by the instant claims. Examiner points to nothing in the Chapman, or in the prior art in as a whole, to suggest the desirability, and thus the obviousness, of making the claimed compounds. In other words, nothing in the prior art teaches or suggests that the Chapman compounds should be modified to arrive at compounds encompassed by the instant claims.

Chapman neither explicitly nor implicitly suggests that particular structural features of the distinct ICE inhibitors should be combined in the specific pattern recited in the instant

claims. In other words, the reference neither teaches nor suggests that a particular first element of the ICE inhibitors should be combined with a particular second element of the ICE inhibitors to arrive at the compounds recited by the instant claims. The reference does not teach all of the choices for these elements, as recited in the claims, or which combinations to use to arrive at the claimed compounds. Thus, Examiner has failed to provide reasons why the artisan of ordinary skill, when confronted with the same problems as the inventors and with no knowledge of the claimed invention, would (***not*** could) select the elements from the cited reference for combination in the manner claimed.

Examiner takes the position that the artisan would be motivated to prepare the compounds allegedly suggested by Chapman for their art-disclosed activity as ICE inhibitors. (Office Action, at top of page 8, first full sentence.) However, the fact that compounds disclosed in Chapman may have activity as ICE inhibitors is not sufficient motivation to make the claimed compounds. The patent must teach or suggest that the particular compounds of the invention should be made, and that when made, the compounds will be useful for the treatment of diseases associated with ICE. As noted above, Chapman contains no such teaching or suggestion.

Rejection of Claims 23, 28 and 29 over Chapman, et al. further in view of Bemis

Claims 23, 28 and 29 are rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent No. 5,430,128 to Chapman, *et al.* ("Chapman") as applied to claims 1, 10, 11, 21, 24-27, 30, and 52-56 , and further in view of U.S. Patent No. 5,843,904 to Bemis, *et al.* ("Bemis"). The Office Action sets forth the allegation that it would have been obvious to use the exemplified ester and other compounds made obvious by Chapman for the treatment of stroke, Alzheimer's disease, and shigellosis based on the teaching of Bemis that ICE inhibitors have utility in treating these disorders.

Applicants respectfully traverse the rejection. Applicants made arguments above to distinguish the Chapman and Bemis patents from the instant claims, and reiterate the substance of those arguments here.

Bemis is directed to compounds that are inhibitors of ICE and to the use of the compounds for the treatment of IL-1 and apoptosis-mediated diseases. The patent neither teaches nor suggests the compounds of the invention. In fact, the compounds of Bemis are significantly structurally distinct from those of the invention, because the Bemis compounds lack the aforementioned structural feature, *i.e.*, $-(CO)CH_2(O_2C)R^2$, found in the claimed compounds. Moreover, there is nothing in the reference that suggests that compounds lacking this feature would be structurally

and functionally equivalent to the claimed compounds, such that one of ordinary skill in the art would be motivated to modify the Bemis compounds to arrive at the claimed compounds, and would reasonably expect them to have the same activity.

Furthermore, Chapman does not make up for the deficiencies of the Bemis patent. The compounds disclosed in Chapman also have the above-mentioned structural feature that the Bemis compounds lack. As there is nothing in either reference that suggests that the compounds lacking this feature would be structurally and functionally equivalent, one of ordinary skill in the art would not be motivated to combine the references.

Column 8, lines 30-41, of Chapman indicates that the compounds disclosed therein are useful for the treatment of interleukin-1 and interleukin -1β mediated or implicated disorders, and specifically lists septic shock, allograft rejection, inflammatory bowel disease and rheumatoid arthritis. There is no mention at all of stroke, Alzheimer's disease and shigellosis. Moreover, there is no mention in the reference that IL-1 has been implicated in stroke, Alzheimer's disease and shigellosis. Thus, absent the teachings of the instant application, one of ordinary skill in the art would have no motivation to combine the references in the manner suggested in the Office Action.

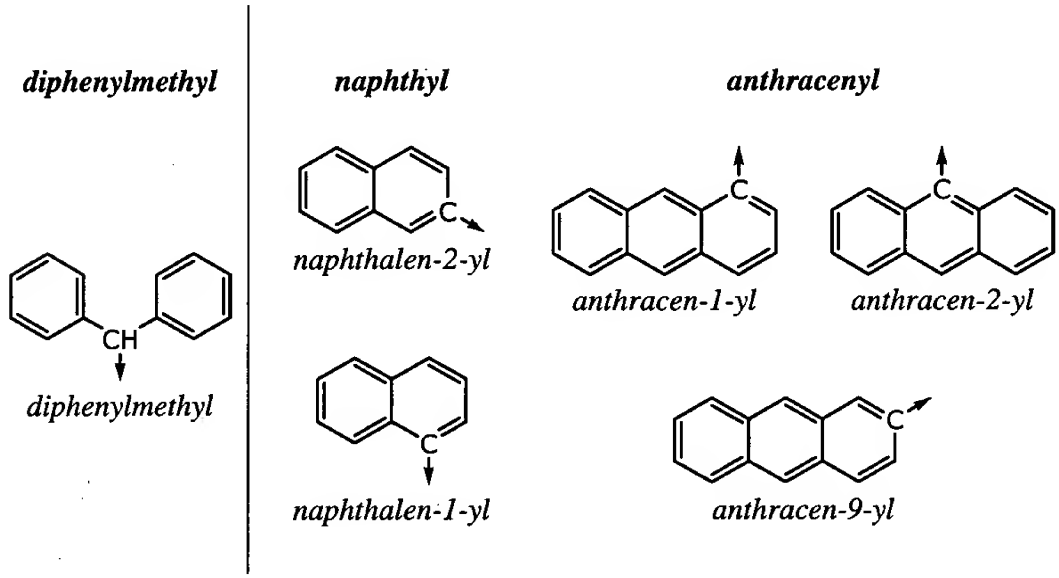
Rejection of Claims 1, 10-12, 21, 24-28, 30, and 55-61 over Heng, et al.

Claims 1, 10-12, 21, 24-28, 30, and 55-61 are rejected under 35 U.S.C. § 103(a) as unpatentable over Heng, *et al.*, EP 618,223 ("Heng"). Applicants respectfully traverse the rejection.

Applicants submit that claims 1, 10-12, 21, 24-28, 30, and 55-61 are patentable under 35 U.S.C. § 103(a) over patent for the reasons of record and for the additional reasons presented below. Applicants presented arguments to distinguish Heng over the claimed invention, under 35 U.S.C. §§ 102 and 103, in their response to the previous Office Action (Paper No. 28) and reiterate the substance of those arguments here to the extent pertinent.

In the first paragraph on page 10 of the Office Action, Examiner alleges that the Heng expressly suggests obvious variants of compound 31 and other compounds disclosed in the reference, focusing on the R^2 substituent of Formula I in the claims (Y_1 in Heng). In particular, Examiner alleges that page 2, lines 45-48, of the reference teaches that an optionally substituted aryl is a function equivalent of diphenylmethyl at this position. Applicants respectfully disagree.

The passage on which Examiner relies states in pertinent part that " Y_1 is a cycloaliphatic residue; optionally substituted aryl; optionally ring substituted diphenylmethyl; piperidino; or optionally substituted mono-, bi- or tricyclic heteroaryl". There is nothing in the passage that teaches that an optionally substituted aryl is a functional equivalent of diphenylmethyl. Each substituent on the list is separated by a semicolon, and there is no Markush language linking the substituents, suggesting that the substituents are related either functionally or structurally, and therefore are equivalents. Thus, one of ordinary skill in the art would interpret this passage to mean that each of the listed substituents are distinct entities. The structure of a diphenylmethyl, naphthyl and anthracyl moieties are illustrated below.



One of ordinary skill in the art will readily appreciate that the structure of diphenylmethyl is quite different from the aromatic fused ring structures of naphthyl and anthracyl, and would have different electronic and steric properties. For example, in the structures depicted above, the aryl rings in the diphenylmethyl are not restricted to being coplanar, unlike the rings in the structures on the right. Accordingly, without more, one of ordinary skill in the art would not consider these structures to be equivalent. The disclosure of Heng does not provide anything the teaches or suggests that diphenylmethyl and, *e.g.*, naphthyl are equivalent.

Moreover, Examiner has focused on a single substituent, namely R^2 of Formula I. However, there are a number of other substituent positions on the structure, with numerous possibilities for each position. Heng neither explicitly nor implicitly suggests that particular

structural features of the distinct ICE inhibitors should be combined in the specific pattern recited in the instant claims. In other words, the reference neither teaches nor suggests that a particular first element of the ICE inhibitors should be combined with a particular second element of the ICE inhibitors of to arrive at the compounds recited by the instant claims, with an expectation that the resulting compound would be useful for treating diseases that involve or are mediated by ICE.

Rejection of Claims 1, 2, 11, 18-21, 24, 25, 27, 30, 52-57and 59-61 over Dolle

Claims 1, 2, 11, 18-21, 24, 25, 27, 30, 52-57and 59-61 are rejected under 35 U.S.C. § 103(a) as unpatentable over Dolle, *et al.*, EP 623,592 ("Dolle"). Applicants respectfully traverse the rejection.

Applicants submit that claims 1, 2, 11, 18-21, 24, 25, 27, 30, 52-57and 59-61 are patentable under 35 U.S.C. § 103(a) over Dolle or the reasons of record and for the additional reasons presented below. Applicants presented arguments to distinguish Dolle over the claimed invention, under 35 U.S.C. §§ 102-103, in their response to the previous Office Action (Paper No. 28) and reiterate the substance of those arguments here to the extent pertinent.

Again, Examiner has focused on a single substituent, namely R^2 of Formula I. However, there are a number of other substituent positions on the structure, with numerous possibilities for each position. The reference must teach or suggest that a benzyl ester, lower cycloalkyl ester or lower alkyl amide ***should*** (***not could***) be made at the particular position in question. The reference neither explicitly nor implicitly suggests that particular structural features of the distinct ICE inhibitors should be combined in the specific pattern recited in the instant claims. In other words, the reference neither teaches nor suggests that a particular first element of the ICE inhibitors should be combined with a particular second element of the ICE inhibitors of to arrive at the compounds recited by the instant claims, with an expectation that the resulting compound would be useful for treating diseases that involve or are mediated by ICE.

Examiner must show that the skilled artisan, confronted with the same problems as Applicants and ***with no knowledge*** of the claimed invention, ***would*** select the elements from Dolle for combination in the manner claimed. All Examiner has done here is merely identify the elements of a claim or their equivalents in the prior art and then, based on the teachings of the instant applications, assert that the claims are obvious. However, this is not sufficient.

Rejection of Claims 1-8, 10-12, 20-21, 24-25, 27, 30 and 52-54 over Dolle in view of Greene

Claims 1-8, 10-12, 20, 21, 24, 25, 27, 30 and 52-54 are rejected under 35 U.S.C. § 103(a) as unpatentable over Dolle, *et al.* (EP 623592) in view Greene (Protecting Groups in Organic Synthesis). Applicants respectfully traverse the rejection.

Dolle was distinguished extensively above and those arguments are reiterated here. Examiner indicates that the reference discloses compounds exemplified in examples 38, 61 and 62 wherein each has a benzyloxy protecting group, a common protecting group. Greene teaches many common amino protecting groups that are advantageously used in multiple step syntheses of organic molecules. Examiner takes the position that it would have been obvious to modify the Dolle compounds of examples 61 or 62 by substituting acetyl for benzyloxycarbonyl.

Greene does not make up for the deficiencies of Dolle. Greene makes no mention of ICE, inhibitors of ICE or pharmaceutical compositions containing inhibitors of ICE to be used in the treatment of diseases involving or mediated by ICE. Moreover, Greene teaches the use of protecting groups in chemical syntheses, and neither teaches or suggests the use of protecting groups in the context of pharmaceutical formulation, administration or pharmacology of therapeutic drugs. Therefore, why would a pharmacologist go to an organic chemist's handbook on protecting groups?

There is nothing in Greene that would suggest substituting benzyloxycarbonyl with acetyl, or why such a substitution would be beneficial or useful in the context of pharmaceutical formulation, administration or pharmacology of therapeutic drugs. The cited references, alone or in combination, neither teach nor suggest that a particular first element of the ICE inhibitors of one reference should be combined with a particular second element of another reference to arrive at the compounds recited by the instant claims. In short, there is nothing in Greene that would suggest combining it with the Dolle reference. Likewise, there is nothing in Dolle that would suggest combining it with Greene.

Rejection of Claims 1, 10-12, 16, 21, 24-28, 30 and 52-61 over Heng in view of Greene

Claims 1, 10-12, 16, 21, 24-28, 30 and 52-61 are rejected under 35 U.S.C. § 103(a) as unpatentable over Heng, *et al.* (EP 618223) in view Greene ("Protecting Groups in Organic Synthesis"). Applicants respectfully traverse the rejection.

Both references were distinguished extensively above and those arguments are reiterated here. Applicants submit that the claims are patentable over Heng and Greene, alone or in

combination, for the same reasons given directly above for the rejection based on Dolle and Greene.

Rejection of Claims 23 and 29 over Heng in view of Bemis

Claims 23 and 29 are rejected under 35 U.S.C. § 103(a) as unpatentable over Heng, *et al.* (EP 618223) as applied to claims 1, 10-12, 16, 21, 24-28, 30, and 55-61, and further in view U.S. Patent No. 5,843,904 to Bemis, *et al.* Applicants respectfully traverse the rejection.

Both references were distinguished extensively above and those arguments are reiterated here. Applicants submit that the claims are patentable over Heng and Bemis, alone or in combination, for the same reasons given above for the rejections based on Thornberry and Bemis, and on Chapman and Bemis.

In view of the foregoing arguments, Applicants respectfully request reconsideration and withdrawal of all rejections of the claims under 35 U.S.C. § 103.

Allowed and Allowable Subject Matter

Applicants acknowledge and thank Examiner Maier for her determination that claims 34, 38-41, and 44-51 are allowed, and that claims 13-15 and 17 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

CONCLUSION

In view of foregoing, entry of the amendments and remarks presented herein, favorable reconsideration and withdrawal of all rejections and objections, and allowance of this application with all the claims as amended herein are respectfully solicited.

If Examiner believes that a telephone conversation with the Applicants' attorney would be helpful in expediting prosecution of this application, Examiner is invited to call the attorney of record at (617) 227-7400.

Respectfully submitted,

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